Aggregate versus day level association between methamphetamine use and HIV medication non-adherence among gay and bisexual men

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Abstract

Methamphetamine use is associated with HIV infection, especially among gay and bisexual men. Methamphetamine use contributes to disease progression both directly, by increasing viral load and damaging the immune system, and indirectly, by decreasing medication adherence. Research examining the association of methamphetamine use and non-adherence has traditionally compared groups of users and nonusers on adherence, compared methamphetamine use between participants above or below some threshold level of adherence (e.g. >90% dose adherence), or examined aggregate relationships. Using Timeline Follow-back procedures, the present study examined aggregate, threshold, and day-level associations of methamphetamine use with non-adherence in 210 HIV-positive gay and bisexual methamphetamine-using men. Methamphetamine use was not associated with adherence behavior at the aggregate-level, but methamphetamine use on a given day was associated with 2.3 times the odds of non-adherence on that day. Threshold results were equivocal. These data suggest that the methamphetamine and non-adherence relationship is complicated: non-adherence is more likely to occur on days in which methamphetamine is used, but participants reported more non-adherence days in which methamphetamine was not used. This seeming paradox generates questions about the selection of analytical techniques and has important implications for behavioral interventions targeting substance use and adherence among HIV-positive individuals.

Keywords

ADHERENCE; METHAMPHETAMINE; METHODS; DAY-LEVEL

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INTRODUCTION

The availability of antiretroviral therapy, or ART, has led to the suppression of HIV, significantly improving the health of those living with HIV (1). Recent research suggests that ART not only prolongs the lives of HIV+ persons, but also helps prevent the spread of HIV by reducing viral load and therefore decreasing infectiousness (2–6). These benefits are contingent upon rates of ART adherence being sufficient to provide continuous prevention against HIV replication. Among the many barriers that exist to proper ART adherence is the abuse of substances (i.e., alcohol and drugs). A number of theories have been articulated regarding the association between substance use and poor adherence, including the lifestyle associated with substance use (7, 8), cognitive impairment (7–12) and the exacerbation of psychiatric issues (8, 11). However, in order to best evaluate the evidence for these theories, it is important to contextualize research findings within the methods most commonly used to examine the association between substance use and non-adherence.

Traditionally, the association between substance use and adherence has been examined in one of three ways: 1) by exploring differences in adherence between substance use groups; 2) by associating a specified threshold adherence level (e.g., less than 90% adherence) with substance use; or 3) by examining the association between aggregate substance use and non-adherence behavior over a certain period. Each of these methods has made an important contribution to the literature, but has different implications for interpretation. Research that examines differences in adherence behavior by substance use groups – using t-tests, ANOVA, or logistic regression, for example – provides information about the qualitative differences between substance users and non-users, or between substance dependent individuals and those who do not meet criteria for dependence. These studies general conclude that substance users are more likely to miss medication than non-users (8, 12–16), and help identify variables that might drive or moderate differences between groups (12). However, such analyses do not address the question of whether the *amount* of drug use makes a difference in non-adherence, and do not usually allow researchers to distinguish between substance use patterns within a particular class of individuals.

Research that compares individuals who meet a particular adherence threshold (e.g., 90% adherence) to those who do not have concluded that greater levels of drug use, and methamphetamine use in specific, is associated with poorer adherence (17–23). These data offer important information for intervention development; however, questions remain about the choice of appropriate thresholds and the durability of proven associations as thresholds shift. At one time, 95% adherence was considered a gold standard for all patients, though results of newer studies suggest that adherence levels as low as 80% (24–27), or even 55% (24, 28) may be sufficient for viral suppression with certain medication regimens. Indeed, studies that utilize the threshold approach vary widely in their chosen cut-offs, with some using 100% (14, 18, 21), 95% (17, 22), 90% (19, 29), or 80% adherence (23, 30). It may be difficult to understand intervention implications in situations in which amount of substance use predicts non-adherence at a particular threshold, but not another.

Investigations that examine linear associations of aggregate substance use and adherence behavior data are perhaps the most straightforward and easiest to interpret; they provide direct information about whether more substance use is correlated with less medication adherence. However, recent review articles reveal that these types of associations are rarely reported (11, 31, 32). One meta-analysis chose to remove any studies that did not stratify participants into discrete categories of substance use or adherence, thus eliminating opportunities to examine the full range of variability (33). One study that reported a linear association used degree of substance dependence, rather than amount of substance use, and found a significant association for one measure of adherence, but not another (34). The lack

of consistent reports of linear associations between amounts of use and adherence rates presents difficulty for those seeking support for the claim that substance use causes missed medications.

Although each of the above methods provides important information about the role of substance use in adherence behavior, none provides information regarding within-person temporal associations (i.e., how does substance use on a given day impact non-adherence on that same day?). A strong association between substance use and non-adherence at the day level suggests different types of intervention strategies than those designed simply to reduce drug use. A few studies have examined day-level associations between alcohol use and adherence, indicating that as the number of drinks on a given day increases, the likelihood of missing medication increases both on that day (35–37) and on the day after drinking (36). However, despite the growing body of literature on multilevel modeling of event-level and day-level data for the association of substance use and other HIV risk behaviors (38), little if any published work has examined the day-level effects of other substances (i.e., drugs) on adherence.

The present study compares three methods of examining the association between substance use and adherence – aggregate/linear, day-level, and threshold – in a sample of HIV-positive methamphetamine users in New York City. In past research, methamphetamine users and abusers demonstrate high levels of HIV medication non-adherence (8, 14, 19, 39), frequent treatment interruptions (40), a lower likelihood of achieving optimal adherence (41), and higher viral loads (42). In qualitative and ethnographic research, methamphetamine users cite their use as a direct cause of ART non-adherence, above and beyond other barriers to adherence such as side effects and complex regimens (7, 43). Methamphetamine use is a particular problem for gay and bisexual men, with rates being 10 to 20 times higher in this group compared to the general population (44, 45). In addition, methamphetamine is consistently shown to be a risk factor for contracting HIV, especially among gay and bisexual men (46–48), due to its association with increased sexual risk behavior (16, 41, 44, 49–53). As recent research underscores the importance of HIV treatment adherence for both secondary and primary HIV prevention, a better understanding of the true association between methamphetamine use and HIV adherence among HIV-positive gay and bisexual men is paramount. In comparing different methods of association, this study is designed to illuminate nuances in the role of methamphetamine use in non-adherence behavior and guide future research.

METHODS

Participants and Procedures

This article presents baseline data collected from gay and bisexual men recruited in the New York City metropolitan area for Project ACE, a randomized clinical trial of a behavioral intervention focused on crystal methamphetamine use and HIV medication adherence. Between August 2008 and December 2011, 210 participants completed a baseline quantitative survey and a face-to-face interview. Participants were recruited through a multi-method approach implemented in diverse geographic areas of New York City using techniques previously effective in the recruitment and enrollment of substance-using gay and bisexual men (54, 55). Eligible participants were biologically male, at least 18 years of age, HIV-positive (confirmed with documentation), currently prescribed an ART medication regimen, and English speaking. Additionally, screening criteria required that participants report at least 3 days of methamphetamine use during the previous 90 days and 1 day in the last 30 days, and a minimum of 3 days of HIV medication non-adherence within the last 30 days. All study participants gave written informed consent and all study procedures were approved by the Institutional Review Board of the City University of New York.

Measures

Participants reported their age, year of HIV diagnosis, race and ethnicity, sexual identity, income, and education level using audio-assisted computer administered self-interviews (ACASI). Drug use and HIV medication adherence data were collected using a 14-day Timeline Follow-back (TLFB) interview (56). A period of 14 days was used to collect two weeks of both weekday and weekend activity so as to capture consistent and inconsistent patterns that may be missed with a shorter assessment period. The TLFB has previously demonstrated good test-retest reliability, convergent validity, and agreement with collateral reports for drug abuse (57) and has been previously utilized with substance-using gay and bisexual men (55, 58–60). In addition, the TLFB has been previously used to measure HIV medication adherence in substance-using populations (61, 62), and adherence data collected with TLFB interviews correlates well with HIV biological markers (10). Interviewers received extensive training in the administration of the TLFB, and demonstrated skills (as evidenced by ongoing quality assurance of audiotapes of the TLFB interviews and supervision) in the development of rapport with participants and remaining non-judgmental in order to facilitate honest self-reports and to respect the values and behaviors of all participants.

An interviewer asked participants to reflect back on the past 14 days, mark memorable events (e.g., vacations, birthdays, paycheck days, parties) on the calendar as anchor points, and then recall day by day whether or not they had used methamphetamine, as well as other drug use, and whether or not they had missed any doses of their HIV medications. This method of data collection allowed us to analyze data at the aggregate level (i.e., number of methamphetamine use days, number of missed medication days) as well as at the day level (for each day, whether methamphetamine was used and whether any doses of HIV medications were not taken).

In addition to the training interviewers received in remaining non-judgmental throughout the data collection process, urine tests of drug use were also obtained to create an environment where participants have less incentive to lie, and to validate the TLFB. In fact, percent concordance between methamphetamine self report and qualitative urine toxicology was 90.1%. This concordance indicates valid self-report as it is as good, or greater, than what has been found for other substances of abuse (63) or stimulants in specific (64).

Data Analysis

Data analysis took place in four steps. First, we examined whether there were differences in the number of days of HIV medication non-adherence by demographic factors, including age, race/ethnicity, sexual identity, income, education level, and years since HIV diagnosis. No significant differences were identified; therefore, no covariates were entered into subsequent models. Second, we examined the *aggregate*-level association between methamphetamine use and adherence (i.e., the association between participants' total number of methamphetamine use days and total number of non-adherence days in the past two weeks). Because the number of days is a positively skewed count variable, we examined this association using a negative binomial regression model. Negative binomial models are capable of modeling skewed count data, which often result in over-dispersion, and provides more accurate estimates of parameters in such cases than the identity or poisson link functions (65, 66).

Third, we examined the *day*-level relationship between methamphetamine use and adherence (i.e., the extent to which using methamphetamine on a given day was associated with increased odds of non-adherence on that day). This day-level association was tested using General Estimating Procedures (GEE), which is an extension of Generalized Linear

Modeling (GLM). GEE is used to model the average response (e.g., non-adherence across days for any given individual) when multiple observations within the units of analysis are correlated (as they are when the data consist of multiple days for each participant). GEE produces robust estimates of regression coefficients and their variances which can be refined by specifying more accurate estimates of the models variance/covariance structure. Using GEE we were able to test whether using methamphetamine on a given day decreases the odds of taking all HIV medications (non-adherence) on that day compared to a day on which methamphetamine was not used.

Finally, we examined the association between number of methamphetamine use days and two commonly used adherence "thresholds": 90% dose adherence and 80% dose adherence in the past 14 days. These data were analyzed using logistic regression, with total number of meth days in the same period (past 14 days) used as a predictor.

RESULTS

Demographics of the sample and descriptive statistics for HIV adherence and substance use variables are listed in Table 1. Participants were, on average, 41 years old, and had been positive for 13.9 years. Most participants identified as gay, were non-White, made less than $20,000 in the past year, and did not have a college education. Participants averaged 4.1 (Median = 2) days of non-adherence, and 2.7 (Median = 2) days of methamphetamine use.

In aggregate analyses using negative binomial regression, number of methamphetamine use days was not significantly associated with the number of days of medication non-adherence, $\beta = .02$, $p = .42$ (Table 2). In contrast, GEE analyses showed a strong day-level association between methamphetamine use and non-adherence behavior. On a day in which a participant used methamphetamine, his odds of non-adherence on that day increased by 2.30 times, compared to a day in which methamphetamine was not used, $p < .001$ (Table 2). In other words, there is no significant *aggregate*-level association between total number of methamphetamine use days and total number of missed medication days in this sample; however, using methamphetamine use on any given day increases the odds of missing medication *on that day* by more than 200%.

Logistic regression analyses of the association between methamphetamine use and adherence threshold groups are presented in Table 3. There was a significant association between days of methamphetamine use and 90% dose adherence, such that for every additional day of methamphetamine use, the odds of being less than 90% adherent increased by 20% (OR = 1.20, $p < .01$). However, there was no significant association between days of methamphetamine use and the 80% dose adherence threshold

In order to better understand the differences between aggregate, day-level, and threshold associations, Figure 1 displays methamphetamine use and adherence data for five study participants. The total number of methamphetamine use days for each participant ranges from 1 (participants #1 and #2) to 5 (participant #5), and the total number of non-adherence days ranges from 2 (participants #1 and #3) to 13 (participant #2). If there were an aggregate-level association between number of methamphetamine use days and non-adherence days, we would expect to see an association between these two numbers for each participant, i.e., as the number of methamphetamine use days increased across participants, we would expect a similar increase in number of non-adherence days. In contrast, among the two participants who reported only one day of methamphetamine use (participant s #1 and #2), one reported the lowest number of missed medication days (2 days), while the other reported the highest number of days (13 days). Similarly, the participant with the highest number of methamphetamine days (participant #5, 5 days), reported fewer non-adherence

days (8 days) than participant #2, who reported only one methamphetamine use day, but 13 non-adherence days.

However, if we examine the percentage of methamphetamine use days in which non-adherence co-occurred, the data tell a different story. For each participant, the percentage of methamphetamine use days that were also non-adherence days ranges from 75%-100%, with four out of five participants missing medication on 100% of their methamphetamine-use days. As such, the difference in the aggregate versus day-level associations between methamphetamine use and non-adherence can be accounted for by the differential pattern of covariation among these behaviors. Because participants miss their medication on both days in which they use methamphetamine and days in which they do not, the aggregate association between these two behaviors is reduced. However, on days in which participants do use methamphetamine, they are much more likely to miss their HIV medication. Therefore, the day-level association between methamphetamine and non-adherence remains strong. In other words, methamphetamine use means non-adherence, but non-adherence does not necessarily mean methamphetamine use.

DISCUSSION

The present study is the first, to our knowledge, to compare aggregate, day-level, and threshold associations between methamphetamine use and HIV medication non-adherence. Although no aggregate relationship was found, a strong day-level association was identified – participants had more than twice the odds of reporting non-adherence to their HIV medications on a day in which they had used methamphetamine. While this finding does not necessarily imply a causal relationship between these behaviors, it suggests that methamphetamine use plays a critical role in adherence behavior for HIV-positive gay and bisexual men at the day-level. In other words, the mechanism of association between methamphetamine use and non-adherence appears to operate in the co-occurrence of these behaviors, rather than in a general atmosphere or life context that makes adherence difficult. These findings have significant implications for both methodological approaches to understanding the intersection between adherence and other problematic health behaviors (in this case, methamphetamine use), as well as for intervention approaches aimed at HIV-positive gay and bisexual men.

Aggregate level data suggest that, among methamphetamine users, it is not necessarily the frequency with which methamphetamine is used that leads to problems with non-adherence. The day-level analyses, however, provide clear evidence of the connection between the two behaviors – methamphetamine use on a given day significantly increases the odds of medication non-adherence on that particular day. Threshold analyses suggest that the number of days of methamphetamine use may distinguish between patients who are 90% adherent and those who are not, but it does not distinguish between patients who meet lower thresholds. The three sets of analyses suggest that the methamphetamine and non-adherence relationship is complicated: non-adherence is more likely to occur on days in which methamphetamine is used, but participants actually reported more non-adherence days in which methamphetamine was not used. As a result, simplistic measures of the frequency of methamphetamine use and the frequency of medication non-adherence are likely to significantly underestimate the nature of the relationship between these two behaviors. Day-level measurement, be it retrospective using calendar-based assessments, or prospective using diary-based or real time measurement tools, may help researchers to more fully understand the relationships across behaviors. That is, understanding the co-occurrence of behaviors requires analysis of their co-occurrence and not simply their association at the aggregate level.

Methodologically, these findings also underscore the importance of examining behavior within specific risk populations. Certainly, studies have shown that methamphetamine users have higher rates of HIV medication non-adherence compared to non-users (8, 14, 19, 40, 41), but these findings suggest that the impact of methamphetamine may occur at two levels. At the day-level, methamphetamine use itself is associated with non-adherence. But reported non-adherence by methamphetamine users even on days in which the drug is not used suggests other mechanisms of association. In other words, all participants in this study had in common the impact of methamphetamine use generally on their adherence, so the differences in adherence between users are likely driven by other non-methamphetamine factors related to non-adherence. For example, there is evidence that methamphetamine damages limbic regions of the brain in a manner that makes methamphetamine users more susceptible to mood disorders (67). In turn, negative affect has been shown to be associated with more frequent stimulant use and lower adherence in HIV-positive stimulant users (68, 69).

Day level analyses could be used to examine the individual differences in reasons for ART non-adherence behavior. The relative impact of other behaviors could be examined relative to the effect of methamphetamine use. Day level data can be combined with person level factors to examine the relative impact and interaction of cognitive performance or mental health. With data collected at the day level it would also be possible to categorize participants based on the percentage of missed medication that co-occurs with methamphetamine use (or any substance of abuse). An examination of a non-adherent drug using population that has a low percentage of missed medication that co-occurs with drug use could illuminate behaviors that adherence interventions could target in addition to drug use to yield a more effective outcome, especially for those who's problems with adherence extend beyond the substance use-missed medication connection.

The fact that HIV medication non-adherence among methamphetamine users is so much more likely to occur on a day in which methamphetamine was used has clear intervention implications. Decreasing the frequency of days in which methamphetamine is used may have limited impact - with the need for high levels (e.g., 90% or better) of adherence to HIV medications (70–73), even a few days of methamphetamine use, and the corresponding strong effect on non-adherence, could result in viral replication and the development of resistance (73, 74). Pharmacologic approaches to treat methamphetamine have generally been found to lack efficacy (32), although one recent study suggests some success with mirtazapine (75). The only published behavioral intervention that has been evaluated with HIV-positive gay and bisexual men, consisting of eight 90-minute sessions of individual therapy, found significant effects on reducing unprotected sex, but not reducing methamphetamine use (76). Similarly, contingency management interventions to treat methamphetamine abuse have shown mixed results, with two trials focused on gay and bisexual men showing significant effects (77, 78), but one recent trial showing none (79). This trial has been called into question due to twice weekly urine testing, allowing a window for those engaged in the treatment condition to possibly use and still receive contingencies. Better results have been identified when contingency management is combined with cognitive behavioral therapy (80, 81), particularly when the therapy is culturally tailored for gay and bisexual men (82, 83). It is important to note that all of these intervention trials involved rather intensive courses of treatment – it is unlikely methamphetamine abuse will be responsive to briefer forms of counseling. For HIV-positive gay and bisexual men in particular, in which multiple behaviors – methamphetamine use, HIV medication adherence, and risky sexual practices – intersect, it is likely that interventions will need to address both motivation and skills-development in order to have the potential for effect.

The current study is not without limitations. Both behaviors of focus - methamphetamine use and HIV medication non-adherence - were self-reported by participants. However, significant training efforts went into creating a non-judgmental environment in which participants were urged to be as honest as possible. In addition, biological markers (urine testing for methamphetamine and viral load and CD4 counts as proxy indicators of adherence) were collected, which could result in participants being more honest in their self-reports. Indeed, the concordance between TLFB self-report and methamphetamine urine toxicology suggests that this sample's self-report data are valid for methamphetamine, at the very least. These data were also collected retrospectively, using the TLFB. It is possible that drug use events create an anchor such that participants are more likely to recall other behaviors on that day. This is in contrast to assessing these behaviors prospectively, using diary-like measures. This method, however, comes with unique problems, foremost being missing data when the participants forget to complete the diary. The sample was entirely self-selected and comprised of HIV-positive gay and bisexual men interested in an intervention trial designed to improve medication adherence and/or reduce methamphetamine use. An Australian study found only 10% of regular methamphetamine users seek treatment (84), so it is not clear to what degree these results would be generalizable to men not presenting for an intervention study. Further, the sample was comprised entirely of men living in a large urban area - although our sample was quite diverse with regard to race and ethnicity, age, education, and years living with HIV.

The study is also limited in that it is not feasible to examine viral load or CD4 count on a day level, thus it is not possible to know if the day level associations are associated with changes in day level biological markers. It is also important to note that an association between a behavior or a psychological state and the likelihood of non-adherence does not ensure high viral loads or drug resistance. Just as one should not suggest that a medical provider withhold prescribing ART to those who are depressed or have some neurocognitive impairment, one should not take the present findings as a reason to withhold medication from a methamphetamine user. In fact, the lack of a more general association between methamphetamine use and adherence, while a strong day level association exists, suggests that the causes of non-adherence are far more varied than simply methamphetamine use, even for methamphetamine users. There is benefit to prescribing ART to methamphetamine users. Indeed, studies have shown that the small negative impact of the cumulative exposure to stimulants on biological HIV outcomes is dwarfed by the large positive effect of the cumulative exposure to ART (85).

Future analyses and studies should consider the duration of the effect of a methamphetamine use day on medication non-adherence. That is, it is possible that methamphetamine use on Saturday not only negatively affects adherence on Saturday, but may also negatively affect adherence on Sunday. In addition, the day-level predictors of non-adherence on non-methamphetamine use days, as well as predictors of adherence on methamphetamine use days should be examined. As such, this study represents the first step in a more comprehensive understanding of the relationship between methamphetamine use and HIV medication non-adherence. In addition, because of the previously identified connections between methamphetamine use and risky sexual behaviors (16, 41, 44, 49–53), and the fact that non-adherence to HIV medications can result in the transmission of drug resistant strains (73, 74, 86, 87), future studies should examine the day-level associations between methamphetamine use, non-adherence, and sexual risk behavior.

Acknowledgments

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	Day Level Data														Aggregate Level Data			
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Meth days	Non-adherence days	Ratio of meth to non-adherence days	% of meth days with non-adherence
Pt #1										✕	⊗				1	2	0.5	100 %
Pt #2		✕	✕	✕	✕	✕	✕	✕	✕	⊗	✕	✕	✕	✕	1	13	0.08	100%
Pt #3											⊗	⊗			2	2	1.0	100%
Pt #4	⊗	⊗			●	⊗									4	3	1.33	75%
Pt #5	✕	⊗	⊗	⊗	⊗	✕					⊗	✕			5	8	0.63	100%

Figure 1.
Comparing Day-Level and Aggregate-Level Data
● = Methamphetamine Use day
✕ = HIV Medication Non-Adherence day
⊗ = Co-occurence of Methamphetamine Use and Non-Adherence day

Table 1

Sample demographics, HIV bio-markers and risk events baseline participants.

	n	**%**
Ethnicity/Race		
Black	70	33.7
White	70	33.7
Latino	54	26.0
Other	14	6.7
Sexual Identity		
Gay	185	88.1
Bi-sexual	23	11.0
Education		
HS Grad or Less	51	.25
Some College	73	.35
College Grad Plus	85	.40
Income		
Lt $20K	148	71.5
GE $20K	59	28.1
Viral Load Failure		
GE 200+	78	37.1
GE 50+	104	49.5

	Mean	**SD**	**Median**	**Range**
Age at Baseline	40.8	8.8	41	24–63
Years HIV Positive	13.9	7.6	11	0–31
HIV RNA(log10)	2.60	1.4	1.67	1.29–6.12
CD4 Count (Absolute)	460	261	451	19–1144
Meth Use Last 14-days	2.7	2.0	2.0	0–14
Missed ART Last 14-days	4.1	4.2	2.0	0–14
Missed ART/Used Meth 14-days	1.2	1.5	1	0–9

Table 2

Differences in Aggregate versus Day Level Analysis of the relationship between Methamphetamine Use and HIV Medication Non-Adherence (n = 210)

Negative Binomial Regression Approach (Aggregate level analysis. Number of methamphetamine use days predicts number of days of medication non-adherence)				
	β	Exp. β	95% CI	p
Intercept	1.34	3.82	3.08–4.74	<.001
Number methamphetamine days	0.02	1.02	0.97–1.08	.42

Likelihood Ratio χ^2 (1, n = 210) = 0.67, p = .42

Generalized Estimated Equation Approach (Day level analysis. Predicts odds of HIV medication non-adherence on a day methamphetamine was used)				
	β	Exp. β	95% CI	p
Intercept	−1.07	0.34	0.31–0.38	<.001
Methamphetamine day	0.83	2.30	1.90–2.78	<.001
Non-methamphetamine day	1	0		

Table 3

Analyses predicting 14 Day ART Dose Adherence Threshold Groups with Total Meth 14 Day Use

	β	*OR*	*CI*	*p*
	≤90 Percent Dose Adherence			
Constant	0.11	0.90		.608
Total Meth 14 Days	0.18	0.83	1.06–1.36	.005
	≤80 Percent Dose Adherence			
Constant	−0.45	1.56		.021
Total Meth 14 Days	0.07	0.94	0.97–1.18	.183

Note: 113 participants (63.3%) reported less than 90% dose adherence; 91 participants (43.3%) reported less than 80% dose adherence.